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Determining the *in vitro* susceptibility of tebipenem, an oral carbapenem, against third-generation cephalosporin-resistant *Escherichia coli* and *Klebsiella pneumoniae* isolated from bloodstream infections

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Background: Antimicrobials for bloodstream infections due to ESBL- and AmpC-producing *Escherichia coli* and *Klebsiella pneumoniae* are significantly limited due to widespread antimicrobial resistance. Tebipenem, an oral carbapenem, exhibits stability against these resistance mechanisms and may prove an attractive alternative.

Methods: The *in vitro* susceptibility of tebipenem was assessed against previously whole-genome sequenced ESBL- and AmpC-producing *E. coli* (274 isolates) and *K. pneumoniae* (42 isolates) derived from bloodstream infections using broth microdilution testing. Resulting tebipenem MICs were compared with those of other carbapenems previously tested against the isolate collection. Tebipenem activity was also compared against those isolates expressing co-resistance to the common oral antibiotics ciprofloxacin and trimethoprim/sulfamethoxazole.

Results: The tebipenem MIC_{90} value was found to be 0.03 mg/L for *E. coli* and 0.125 mg/L for *K. pneumoniae*. For *E. coli*, the tebipenem MIC_{90} value was equivalent to that of meropenem, 2-fold lower than that of doripenem, and 8-fold and 4-fold lower than that of imipenem and ertapenem, respectively. For *K. pneumoniae*, the tebipenem MIC_{90} value was 2-fold higher than that of meropenem, equivalent to that of doripenem, and 4-fold and 2-fold lower than that of imipenem and ertapenem, respectively. Tebipenem MICs were also unaffected by the expression of co-resistance to ciprofloxacin and trimethoprim/sulfamethoxazole.

Conclusions: The *in vitro* activity of tebipenem was unaffected by the production of ESBL and AmpC enzymes. Tebipenem also retained its activity against those isolates expressing co-resistance to ciprofloxacin and trimethoprim/sulfamethoxazole. These findings therefore highlight tebipenem as a potential option for the treatment of invasive MDR infections.

Introduction

Bloodstream infections (BSIs) are a significant source of morbidity and mortality worldwide.[1] Of those that originate from urinary tract infections (UTIs), the most common causative agents of BSIs are the members of the Enterobacterales order, *Escherichia coli* and *Klebsiella pneumoniae*.[2–4] The third-generation cephalosporin (3GC) subclass of the β-lactam antimicrobial family has often been preferred for the treatment of infections caused by these organisms but overuse and subsequent selection pressure has led to widespread antimicrobial resistance (AMR) amongst these species towards this versatile class of antibiotics.[5,6]

Resistance to 3GCs is primarily conferred via the production of ESBL enzymes, especially the clinically significant CTX-M-type, which is regarded as the most widely disseminated ESBL and whose spread has been broadly attributed to the *E. coli* lineage,

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ST131, a highly virulent and transmissible clone.[7–10] AmpC-type β-lactamases also contribute towards 3GC resistance with enzyme production being either plasmid-mediated (pAmpC) or due to the overexpression of the *ampC* gene.[11,12] Furthermore, 3GC-resistant *E. coli* and *K. pneumoniae* often possess additional genes encoding resistance to multiple other antimicrobials such as fluoroquinolones, aminoglycosides and trimethoprim/sulfamethoxazole, thus resulting in MDR bacteria.[12,13]

A global increase in the prevalence of 3GC-resistant *E. coli* and *K. pneumoniae* has been observed within both nosocomial and community settings over the last two decades and this invites significant concern as it severely limits the availability of treatment options for MDR BSIs.[2] Carbapenems are first-line treatment for infections caused by these organisms as they exhibit the greatest stability towards ESBL- and AmpC-mediated resistance and have been associated with excellent clinical outcomes.[14] Therefore, further additions to this antimicrobial subclass would prove invaluable for the treatment of MDR BSIs.

Tebipenem/pivoxil hydrobromide is an orally bioavailable novel carbapenem prodrug that was approved in Japan in 2009 for paediatric respiratory infections.[15] It was in development by Spero Therapeutics for the treatment of complicated UTIs, including acute pyelonephritis, but a recent re-analysis of the original randomized controlled trial by the US FDA has interrupted its pathway to registration until completion of further clinical studies.[16,17] Tebipenem—the active conformation of the prodrug tebipenem/pivoxil—possesses potent *in vitro* activity against 3GC-resistant *E. coli* and *K. pneumoniae* but is less active against *Pseudomonas aeruginosa*.[18,19] These promising results, together with its convenient oral formulation, therefore highlight the potential for tebipenem as an option for the treatment of uncomplicated episodes of BSIs due to 3GC-resistant *E. coli* and *K. pneumoniae* within a community setting. Consequently, tebipenem may also provide an attractive alternative to traditional non-β-lactam oral step-down options such as ciprofloxacin and trimethoprim/sulfamethoxazole, since 3GC-resistant *E. coli* and *K. pneumoniae* often exhibit high rates of resistance towards these long-preferred step-down antimicrobials.[20–22]

However, there is currently a lack of data to support the use of tebipenem for the treatment of BSIs caused by these MDR organisms. Therefore, the primary aim of this study was to assess the *in vitro* susceptibility to tebipenem of carbapenem-susceptible *E. coli* and *K. pneumoniae* derived from BSIs, expressing 3GC resistance conferred by ESBLs, AmpC overexpression or pAmpCs as assessed via molecular characterization. The activity of tebipenem was also compared with those of other commercially available carbapenems. Additionally, the activity of tebipenem against selected strains within the tested collection expressing co-resistance to ciprofloxacin and trimethoprim/sulfamethoxazole was also assessed in order to ascertain the suitability of tebipenem as a potential alternative to these traditional oral options. Although there has been renewed interest in the use of fosfomycin for the treatment of bacteraemia due to MDR *E. coli*,[23] several studies have reported an increased likelihood of treatment failure with regard to *K. pneumoniae* and, consequently, caution in the use of fosfomycin for such infections.[24,25]

Materials and methods

Bacterial isolates

Three hundred and sixteen clinical BSI isolates consisting of *E. coli* (274 isolates) and *K. pneumoniae* (42 isolates) expressing phenotypic 3GC resistance and carbapenem (meropenem) susceptibility, acquired between 2014 and 2016 from the MERINO trial,[26] were tested (UTI source = 64%, community-onset infections = 78%). The isolates were sourced from Australia ($n = 74$), Canada ($n = 2$), Italy ($n = 6$), Lebanon ($n = 12$), New Zealand ($n = 19$), Saudi Arabia ($n = 21$), Singapore ($n = 136$), South Africa ($n = 8$) and Turkey ($n = 38$). All isolates were stored in 30% (vol/vol) glycerol stock at −80°C at the University of Queensland Centre for Clinical Research. The identification of bacterial species, 3GC resistance and carbapenem susceptibility had been conducted during the MERINO trial microbiological studies as previously described.[26] Furthermore, isolates had also undergone WGS and *in silico* analysis as previously described for the characterization of β-lactamase composition (ESBL, overexpressed AmpC, pAmpC).[26] Isolate specific β-lactamase characterization can be found in Table S1, available as Supplementary data at *JAC* Online.

Antimicrobial susceptibility testing

The *in vitro* susceptibility of isolates to tebipenem was assessed through MICs obtained via broth microdilution (BMD) testing performed as per the International Organization for Standardization standard 20776-1:2019.[27]

Tebipenem (Spero Therapeutics) dry powder was dissolved in deionized water to prepare a 1000 mg/L stock solution, which was further diluted in BBL™ CAMHB (Becton, Dickinson and Company) to achieve eleven doubling dilutions of final concentrations ranging between 0.004 and 4 mg/L (after addition of bacterial inoculum). Concentrations within the selected range were consistent with tebipenem MICs reached by 3GC-resistant *E. coli* and *K. pneumoniae* in previous BMD studies.[19,28]

The dilutions were dispensed into 96-well plates (Thermo Fisher Scientific) using the Hamilton Microlab STAR Liquid Handling system (Hamilton Company). All plates contained both negative and positive control wells. Prepared plates were stored at −80°C and thawed for 2 h prior to use.

All isolates were cultured on 5% horse blood agar (Edwards Group) and incubated at 37°C for 18–24 h, prior to the preparation of a 0.5 McFarland solution in 0.9% sterile saline using the direct colony suspension method. The resulting inoculum was further diluted in CAMHB and added to the plates to give a final cell concentration of 5×10^5 cfu/mL. All isolates were tested in triplicate.

Quality assurance was performed concurrently for every tested plate in accordance with CLSI M100 guidelines,[29] using the quality control strains *E. coli* (ATCC 25922), *Staphylococcus aureus* (ATCC 29213) and *P. aeruginosa* (ATCC 27853). A purity check and colony count were also performed for both test isolates and quality strains. Inoculated plates were incubated at 35°C for 18–20 h and MIC endpoints were determined visually using the Sensititre™ Manual Viewbox (Thermo Fisher Scientific).

Data analysis

The median from the triplicate set of values for each isolate was selected as the tebipenem MIC.

The MIC_{50} and MIC_{90}, which are the MICs at which 50% and 90% of the isolates are inhibited, respectively, were calculated for *E. coli* and *K. pneumoniae* isolates separately.

Comparison of tebipenem MICs with those of other carbapenems

Tebipenem $MIC_{50/90}$ values were compared against the $MIC_{50/90}$ values of other carbapenems—meropenem, imipenem, doripenem and

ertapenem—which were previously acquired for the isolates during the MERINO trial microbiological studies via BMD testing,[26] using custom-made Sensititre™ plates (Thermo Fisher Scientific) tested according to manufacturer's instructions. The concentrations tested ranged between 0.015 and 16 mg/L for meropenem, 0.06 and 16 mg/L for imipenem, 0.03 and 8 mg/L for doripenem and 0.015 and 4 mg/L for ertapenem.

Characterization of tebipenem MICs against isolates expressing co-resistance to ciprofloxacin and trimethoprim/sulfamethoxazole

Tebipenem MICs for *E. coli* and *K. pneumoniae* were collectively categorized against isolates expressing co-resistance to ciprofloxacin and trimethoprim/sulfamethoxazole using the statistical software R.[30] The associated package ggplot2 was used to generate figures accordingly.[31]

Results

Tebipenem MICs for both *E. coli* and *K. pneumoniae* isolates ranged between 0.015 and 0.25 mg/L (Table S1). Tebipenem $MIC_{50/90}$ values against *E. coli* were 0.03/0.03 and 0.03/0.125 mg/L against *K. pneumoniae* (Table 1).

Comparison of tebipenem MICs with those of other carbapenems

Tebipenem $MIC_{50/90}$ values were compared with $MIC_{50/90}$ values of other clinically available carbapenems that were previously acquired for the isolate collection (Table 1). For *E. coli* isolates, tebipenem exhibited equivalent $MIC_{50/90}$ (0.03/0.03 mg/L) values to those of meropenem and an MIC_{90} value 2-fold lower than that of doripenem (0.06 mg/L) and 4-fold lower than that of ertapenem (0.12 mg/L). Tebipenem $MIC_{50/90}$ values were 8-fold lower than that of imipenem (0.25/0.25 mg/L).

For *K. pneumoniae*, tebipenem exhibited an equivalent MIC_{50} value (0.03 mg/L) but a 2-fold higher MIC_{90} (0.125 mg/L) value than that of meropenem (0.06 mg/L). The tebipenem MIC_{50} value was 2-fold lower than that of doripenem and ertapenem (0.06 mg/L) and 8-fold lower than that of imipenem (0.25 mg/L). The tebipenem MIC_{90} value (0.125 mg/L) was 2-fold lower than that of ertapenem (0.25 mg/L), 4-fold lower than that of imipenem (0.5 mg/L) but equivalent to that of doripenem (0.12 mg/L).

Table 1. MICs of tebipenem and comparator carbapenems against 3GC-resistant *E. coli* and *K. pneumoniae*

	E. coli (mg/L)		*K. pneumoniae* (mg/L)	
Antimicrobial	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
Tebipenem	0.03	0.03	0.03	0.125
Meropenem	0.03	0.03	0.03	0.06
Imipenem	0.25	0.25	0.25	0.5
Doripenem	0.03	0.06	0.06	0.12
Ertapenem	0.03	0.12	0.06	0.25

Characterization of tebipenem MICs for isolates expressing co-resistance to ciprofloxacin and trimethoprim/sulfamethoxazole

Tebipenem MICs were categorized according to the expression of co-resistance to the common oral antimicrobials ciprofloxacin and trimethoprim/sulfamethoxazole (Figure 1). A majority of isolates were inhibited at an MIC of 0.03 mg/L and many of them carried co-resistance to both ciprofloxacin and trimethoprim/sulfamethoxazole, followed by ciprofloxacin alone, together with a smaller proportion carrying resistance to trimethoprim/sulfamethoxazole only. Similar grouping patterns were observed at MICs of 0.015, 0.06 and 0.125 mg/L. A number of isolates inhibited at a tebipenem MIC of 0.25 mg/L were resistant to trimethoprim/sulfamethoxazole alone while several expressed co-resistance to both trimethoprim/sulfamethoxazole and ciprofloxacin. Several isolates were susceptible to both antimicrobials.

Discussion

BSIs due to 3GC-resistant *E. coli* and *K. pneumoniae* are associated with a high health and economic cost due to the widespread prevalence of AMR towards most agents that are available to combat them. Tebipenem/pivoxil hydrobromide may therefore prove an invaluable addition to the armamentarium as it combines the potent activity of a carbapenem together with a convenient oral formulation. However, there is a noticeable lack of literature regarding the effectiveness of tebipenem against 3GC-resistant *E. coli* and *K. pneumoniae* isolated from BSIs, which this study aimed to address.

As expected, tebipenem exhibited excellent activity against all isolates in this study, with MIC_{90} values of ≤0.125 mg/L for both species tested, thereby confirming the *in vitro* susceptibility of tebipenem against 3GC-resistant *E. coli* and *K. pneumoniae*. Furthermore, as per the tebipenem provisional susceptibility breakpoint of ≤0.125 mg/L generally utilized for Gram-negative organisms,[32,33] a majority of the isolates in the current study can be regarded as provisionally susceptible, thus demonstrating the stability of tebipenem against hydrolysis by ESBL and AmpC enzymes. A number of isolates ($n=3$) also exhibited an MIC of 0.25 mg/L (Table S1) but without the availability of established susceptibility breakpoints, it is impossible to make any further interpretations about the clinical significance of these findings.

When the MIC_{90} values of tebipenem were compared with those of other commercially available carbapenems (Table 1), tebipenem demonstrated equivalent activity to meropenem and 2-fold greater activity than doripenem against *E. coli* and equivalent activity to doripenem against *K. pneumoniae*. Tebipenem was also found to exhibit 2-fold lower activity than meropenem against *K. pneumoniae* but this is most likely due to the availability of a smaller number of *K. pneumoniae* isolates within the collection for testing, thus resulting in a limited distribution of MICs and, therefore, a higher MIC_{90} value. The activity of tebipenem was also found to be 4- to 8-fold greater than the activity of ertapenem and imipenem, respectively, against *E. coli*. Against *K. pneumoniae* isolates, tebipenem activity was found to be 2- to 4-fold greater than that of ertapenem and imipenem, respectively. A similar trend in activity between the

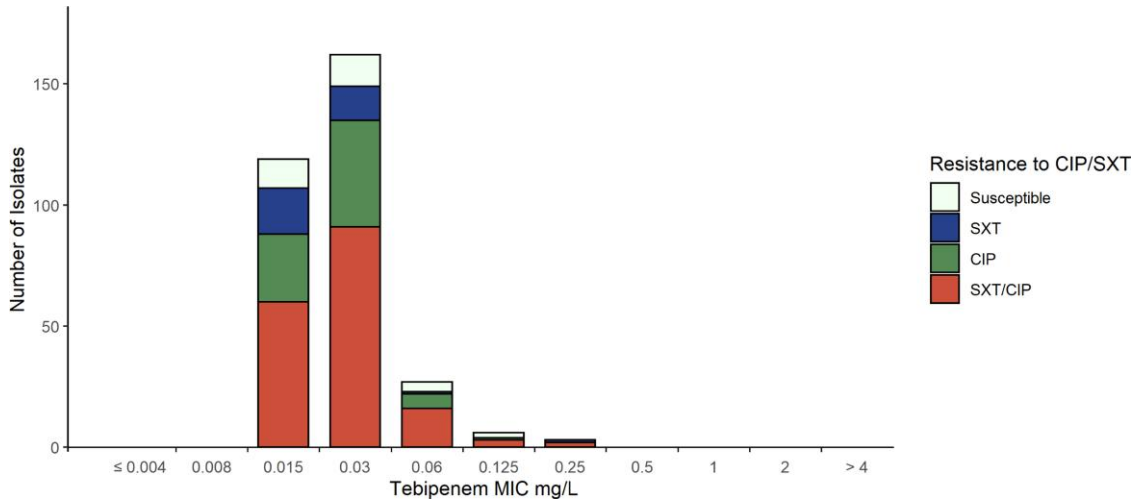

Figure 1. Distribution of tebipenem MICs in E. coli and K. pneumoniae isolates expressing co-resistance to the common oral antibiotics ciprofloxacin (CIP) and trimethoprim/sulphamethoxazole (SXT).

aforementioned carbapenems was also obtained in previous studies.[19,28]

Similarly, the MIC distribution also showed that the activity of tebipenem was unaffected by the presence of co-resistance to the common non-β-lactam oral treatment options, ciprofloxacin and trimethoprim/sulfamethoxazole (Figure 1). The effectiveness of tebipenem against such resistance mechanisms therefore support its use as a successful form of oral step-down therapy and also as a potential treatment option for non-severe episodes of BSIs due to 3GC-resistant *E. coli* and *K. pneumoniae* within a community setting. BSIs due to such MDR Enterobacterales are known to frequently originate from UTIs, mostly carry the CTX-M-type ESBL and are predominantly caused by ST131 *E. coli*; these distributions were also observed among the MERINO trial isolates,[26] which were primarily derived from community-onset BSIs. In this study, tebipenem exhibited potent activity against these commonly isolated strains and resistance mechanisms, which together with its oral formulation may prove extremely beneficial for community-based treatment. Additionally, the narrower spectrum of activity possessed by tebipenem can be well utilized to treat BSIs acquired in the community where Enterobacterales predominate and infections due to *P. aeruginosa* are rare.[34]

The current study serves to contribute to the growing literature assessing the *in vitro* activity of tebipenem against 3GC-resistant *E. coli* and *K. pneumoniae* derived from BSIs. It had several strengths—the first of which was the assessment of isolates from nine different countries. Resistance patterns are known to vary between locations,[35] and the inclusion of a sizeable multinational isolate collection enabled the assessment of the effectiveness of tebipenem against a considerable internationally representative sample. Secondly, antimicrobial activity was assessed against numerous AMR genes and the integration of genotypic and phenotypic data enabled the development of a comprehensive picture of the *in vitro* activity of tebipenem against MDR *E. coli* and *K. pneumoniae*.

However, the study also had several limitations. The number of *K. pneumoniae* isolates was significantly less than that of *E. coli*, and this may have led to a less accurate representation of tebipenem activity against the species. Furthermore, the MICs of the comparator carbapenems were acquired via custom-made Sensititre™ plates, unlike the tebipenem MICs, which were obtained through plates prepared via an in-house liquid-handling system. There was also no determination of the impact of the inoculum effect on the *in vitro* activity of tebipenem as it was understood as a phenomenon that was less likely to be observed with carbapenems.[36] However, a study reported a decrease in the antibacterial activity of tebipenem against reference *E. coli* and *K. pneumoniae* strains with increasing inoculum size,[28] thus highlighting the need for further study concerning the inoculum effect on tebipenem with regard to clinical isolates.

Nevertheless, the results generated from this study have significant implications for the treatment of BSIs caused by 3GC-resistant Enterobacterales. We managed to confirm the *in vitro* susceptibility of tebipenem against 3GC-resistant *E. coli* and *K. pneumoniae*, thereby providing supporting data towards the introduction of a novel treatment form for MDR BSIs in the form of an oral carbapenem. Such an option can prove to be extremely convenient and cost-effective as the management of such infections outside of a hospital setting can lead to reduced healthcare-associated costs.[15] Furthermore, the introduction of tebipenem/pivoxil hydrobromide into clinical practice can significantly limit the unnecessary prolonged use of IV carbapenems, which may carry risks of thrombophlebitis and vascular access-related infections.

As tebipenem/pivoxil hydrobromide appears to confer a wide range of benefits, the need for future study regarding its effectiveness in humans in addition to further *in vitro* research is most certainly warranted to support its use within a clinical context.

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Supplementary data

Table S1 is available as Supplementary data at *JAC* Online.

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